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Comparison of procaine penicillin alone with ampicillin plus probenecid in the treatment of gonorrhoea in the male

R. B. ROY AND S. M. LAIRD
Royal Victoria Hospital, Bournemouth, Hants.

An effective single-dose, oral treatment for gonorrhoea would help to relieve pressure in a staff-starved specialty coping with busy clinics, especially if it also reduced the incidence of subsequent non-gonococcal urethritis (NGU) in males. NGU after cure of gonorrhoea is not uncommon. Csonka (1967) found an incidence of 22 per cent. after effective penicillin treatment of gonorrhoea but only 6 per cent. when tetracycline was used. Penicillin has little, if any, effect on NGU. The cure rate obtained in gonorrhoea treated with procaine penicillin varies from country to country and even in the same area from time to time. This varying success is due to the prevalence of relatively insensitive strains of *N. gonorrhoeae* and such strains require a higher level of penicillin if cure is to be obtained. Ampicillin is acid-stable, absorption after oral administration is good and little influenced by food, and it is relatively cheap, and non-toxic; an oral dose of 1 g. produces a peak plasma level after 2 hrs of about 6 μg./ml. (Goodman and Gilman, 1970). Normally about one-quarter of an oral dose is cleared by the kidney in the first 12 hrs, but this excretion can be reduced and delayed by the concurrent use of probenecid. Ampicillin is bactericidal during the logarithmic growth phase of *N. gonorrhoeae* so it is important to prolong the period of an effective level of penicillin in the plasma. From Denmark, Brø-Jorgensen and Jensen (1971) reported a failure rate of only 1·9 per cent. using this combined treatment. It was, therefore, decided to evaluate the efficacy of a single oral treatment combining ampicillin and probenecid.

Material and methods

Alternate male patients with gonorrhoea, in a series of 252 consecutive cases, were treated either with one intramuscular injection of 1·2 m.u. aqueous procaine penicillin or with 1 g. ampicillin plus 1 g. probenecid swallowed with water under supervision in the clinic. The diagnosis was based on Gram-stained smears and culture of urethral discharge. Treatment was given on the first attendance without awaiting the culture results. Blood was taken for serological tests for syphilis at the first visit, 4 to 6 weeks later, and, where possible, after 3 months. Patients were told to avoid alcohol and sexual intercourse, but doubtless these restrictions were not always observed. Each patient treated on Monday, Tuesday, or Wednesday was asked to re-attend in 48 hours; those treated on a Thursday or Friday were seen again on the following Monday (*i.e.* 3 or 4 days later). Every patient was instructed to avoid passing urine for 3 to 4 hrs before re-attending for examination. Patients were subsequently asked to attend approximately 7, 14, 21, 28, and 42 days after the date of treatment. If any urethral discharge was found, smears and cultures were taken and the findings in the 2-glass urine test at each visit were noted. Alcohol was allowed after 2 weeks if the urethritis had settled. Wherever possible the female partner was examined and, if *T. vaginalis* was found, the male patient was treated with metronidazole or nimorazole in standard dosage.

Patients regarded as failures were generally re-treated with the alternative regime unless or until the results of sensitivity tests indicated another antibiotic. The distinction between relapse and re-infection is sometimes difficult and the criteria used have been discussed widely.

In the present study, all recurrences within 14 days have been recorded as treatment failures (Table III). Two cases have been classified as re-infections as the recurrences occurred after 14 days after further sexual exposure with a consort in whom the presence of gonorrhoea was subsequently confirmed and in whom the original treatment regime was again effective, not only in the two men, but also in the female partners.

Results

Amongst the 252 consecutive male patients with gonorrhoea allotted alternately to one or other of the two treatment regimes, two had rectal infection only and five others had complications which required more prolonged therapy. Excluding these seven patients, 125 received ampicillin and probenecid (AB) and 120 had a single injection of 1·2 m.u. aqueous procaine penicillin (PP). Nine of these patients did not re-attend even once and have been excluded from

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the comparison of the two treatment regimes (Table I). The comparison is therefore between the results obtained in 116 patients (PP group) and 120 (AB group). Table I also shows the number of patients attending for subsequent follow-up examinations. Table II shows the numbers treated subsequently for non-specific urethritis (NSU) and the numbers given metronidazole or nimorazole as a result of the finding of *T. vaginalis* in the female consorts.

TABLE I *Number of patients in each treatment group and their follow-up*

Number of days after treatment	*Number of patients followed after treatment with*	
	Procaine penicillin	*Ampicillin and probenecid*
0	120	125
2– 4	116	120
7–10	99	98
14–17	80	79
21–28	60	61
29–42	24	28
43–56	18	20
3 mths or more	16	16

TABLE II *Number of patients requiring subsequent treatment for NSU and numbers treated as* T. vaginalis *contacts*

Initial treatment	*Treated for subsequent NSU*		*Treated as* T. vaginalis *conacts*	
	No.	*Per cent.*	*No.*	*Per cent.*
Procaine penicillin	39	33·6	14	12·1
Ampicillin plus probenecid	29	24·1	19	15·8

Failure to respond to treatment occurred in seven (6 per cent.) of 116 PP cases and in five (4·2 per cent.) of 120 AB cases (Table III). Two men, one in each primary treatment group, failed with both treatment schedules and were infected with the same strain which was relatively insensitive to penicillin; one of these men was infected in the U.S.A. and on his return to Bournemouth infected his girl-friend who in turn infected the second man. In each of these three people the *N. gonorrhoeae* cultured showed reduced sensitivity to penicillin and tetracycline and all three were treated successfully with 2 g. kanamycin. If these two men are excluded from the analysis, the cure rates of the primary treatment regimes improve to 94·8 per cent. (PP) and 96·7 per cent. (AB).

One man who failed with one injection (PP) was unable to swallow the oral (AB) regime but responded to two injections of PP given on consecutive days. This man was the only one who had difficulty in swallowing the oral therapy and none so treated reported vomiting. Unexpectedly, no case of ampicillin rash was encountered.

TABLE III *Number of failures and time of diagnosis*

Time of failure (days)		*Number of failures*	
		PP Group	*AB Group*
2		2[a]	3[a]
4		1	
7		3	2
10		1	
Total failures	No.	7	5
	Per cent.	6	4·2

[a]Both groups include one man infected with same strain of *N. gonorrhoeae* (from U.S.A.) which showed reduced sensitivity to penicillin and tetracycline, but was sensitive to kanamycin

Discussion

This study of the effectiveness of a single dose oral treatment, using 1 g. ampicillin and 1 g. probenecid, for uncomplicated urethral gonorrhoea in males was carried out at the Royal Victoria Hospital, Bournemouth, during 1972. The 96 per cent. cure rate obtained is very close to the 98 per cent. recently reported by Brø-Jorgensen and Jensen (1971) in Denmark. These high cure rates may not be achieved in other countries, or indeed in the large conurbations of the U.K., because of the varying incidence of highly insensitive strains of *N. gonorrhoeae*. The results of the oral regime were compared with those obtained in alternate patients with one injection of a relatively small amount of aqueous procaine penicillin (1·2 m.u.). The latter regime gave equally good results (94 per cent. cure rate), but the oral treatment given under supervision is more acceptable to injection-shy patients and saves the time of hard-pressed staff. Our results with the same oral regime in female cases of gonorrhoea, not reported here, are also excellent, and this has now become our standard treatment. It may well be that, with variation in the sensitivity pattern of strains of *N. gonorrhoeae* in the future, this single-treatment regime may become less successful, and regular monitoring of its performance must be maintained by study of the clinical failure rate and the penicillin sensitivity of the strains grown on culture.

Evaluation of any new antibiotic regime for gonorrhoea has been complicated since the introduction of sulpha drugs (Laird, 1940) by the difficulty of correctly classifying the recurrence of symptoms as relapse or re-infection. Curtis and Wilkinson (1958),

from studies of the sensitivity pattern of *N. gonorrhoeae* in previously untreated patients and in cases requiring re-treatment after the use of penicillin, concluded that all recurrences within 7 days of treatment, irrespective of further sexual exposure, are relapses, while recurrences after 7 days are re-infections. This conclusion was also adopted in the M.R.C. Interim Report (1961), but reservations have been expressed by Willcox (1964) and Evans (1966). In 'repeaters' especially, incubation periods over 5 days are not uncommon and in an occasional case a period of just over 10 days has seemed genuine (Laird, 1963). All recurrences in this study within 14 days of treatment have thus been conservatively classified as failures.

At least one post-treatment examination was made in all but nine of the 245 cases studied (*i.e.* in 96·3 per cent.). It may well be that non-attendance suggests clinical cure, especially with the high cure-rate found in those who did attend for follow-up, but these nine cases were excluded when calculating the cure-rates.

NSU may persist after effective penicillin treatment of urethral gonorrhoea in men or it may develop during the next few weeks; Csonka (1967) reported an incidence of 22 per cent. As the symptoms are mild and the signs minimal, its incidence will parallel the carefulness of the follow-up examinations. In this study, 39 (33·6 per cent.) in the PP group and 29 (24·1 per cent.) in the AB group required treatment for NSU. These percentages seem high, particularly as men whose consorts were found to have *T. vaginalis* were given a standard course of metronidazole or nimorazole (12·1 per cent. of the PP group and 15·8 per cent. of the AB group). On balance, the AB regime seems marginally more effective in this respect than the PP regime.

Summary

Consecutive male cases of gonorrhoea were allotted alternately to one of two treatment regimes: 1·2 m.u. aqueous procaine penicillin (PP group) or 1 g. ampicillin plus 1 g. probenecid given orally under supervision (AB group). Of 236 cases who re-attended at least once after treatment, 94 per cent. of the PP group and 96 per cent. of the AB group were cured. The incidence of post-treatment NSU was lower in the AB group and side-effects were absent in both groups. It is concluded that, at the present time in the Bournemouth area, this single-dose ampicillin and probenecid treatment given under supervision is highly effective, very acceptable to the patients, and saves the time of hard-pressed nursing staff.

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Comparaison de la pénicilline-procaïne employée seule et de l'association ampicilline-probénécide dans le traitement de la gonococcïe masculine

SOMMAIRE

Des cas consécutifs de gonococcie masculine furent soumis à l'un ou l'autre de deux schémas thérapeutiques: 1,2 m.u. de pénicilline-procaïne aqueuse (Groupe PP) ou 1 g d'ampicilline plus 1 g de probénécide donné sous surveillance par voie buccale (groupe AB).

Pour les 236 cas qui revinrent consulter au moins une fois après le traitement, 94 pour cent furent guéris dans le groupe PP et 96 pour cent dans le groupe AB. L'incidence des urétrites non spécifiques après traitement fut plus faible dans le groupe AB et les effets secondaires furent absents dans les deux groupes. On conclut qu'à l'heure actuelle, dans la région de Bournemouth, une dose unique d'ampicilline plus probénécide donnée sous surveillance est hautement efficace, très bien acceptée par les malades, et economise le temps d'un personnel soignant très occupé.